REMARKS

Status of the claims:

With the above amendment, claims 1-10, 17-22, 25, 26, 28-30, 33, 38, and 39 are pending and ready for further action on the merits. No new matter has been added by way of the amendment to the written description. Support for the amendment comes from page 3, line 18 *et seq*. Entry of the amendment and reconsideration is respectfully requested in light of the following remarks.

Inquiry regarding claim 39

A rejection for claim 39 was not found in the Office Action of January 29, 2002 yet on the accompanying "Office Action Summary" form, it shows that claim 39 is rejected. Thus, Applicants inquire as to the status of claim 39.

Specification Objections

The Examiner has objected to the language "recombinant DNA molecule encoding or otherwise causing the expression of". The Examiner asserts that changing the expression "recombinant DNA molecule encoding or otherwise causing the expression of" to "recombinant DNA molecule encoding and causing the expression of" will obviate the objection. Applicants traverse for the

reasons explained in the section titled "Rejections under 35 U.S.C. § 112, second paragraph". (See below).

Drawings

Applicants will file formal drawings upon the receipt of a Notice of Allowance.

Rejections under 35 USC §112, second paragraph

Claims 1-10, 17-22, 28-30, 33 and 38 have been rejected under 35 USC §112, second paragraph as being indefinite.

Claim 1 is rejected for reciting "at least one recombinant DNA molecule encoding or otherwise causing the expression of at least one enzyme". This rejection is traversed for the following reasons.

The wording ". . . recombinant DNA molecule encoding or otherwise causing the expression of a gene." includes the possibility that the recombinant DNA molecule does not encode the complete open reading frame of a gene, but replaces the natural promoter of an endogenous gene with a promoter that causes stronger expression or expression under different conditions. This idea is set out in the paragraph starting on line 11 of page 26. This is particularly important in this invention, because as is explained in the Background (see the paragraph beginning on line 6 of page 5), host cells may

naturally contain both genes for suitable pairs of dehydrogenases, but simultaneous expression of both dehydrogenases in the same cell compartment is prevented. This can be changed by changing the promoter or the targeting sequence using a recombinant DNA molecule that does not encode the dehydrogenase.

Accordingly, Applicants assert that when claim 1 is read in light of the specification, it is neither vague nor indefinite. Withdrawal of the rejection is warranted and respectfully requested.

Claim 7 has also been rejected under 35 USC §112, second paragraph as being indefinite. The Examiner has maintained the rejection of claim 7 for the use of the phrase "required metabolic capacity". In the amendment of November 19, 2001, claim 7 had been amended so that it no longer contained this term. Accordingly, Applicants assert that the rejection is inapposite. Withdrawal of the rejections is warranted and respectfully requested.

Rejections under 35 USC §112, first paragraph

Claims 1-10, 17-22, 28-30, 33 and 38 have been rejected under 35 USC §112, first paragraph as allegedly lacking complete enablement. The Examiner asserts that while the specification is enabled for making ethanol on an industrial scale, that the

specification is not enabled for making other chemical compounds that are more reduced than pyruvate. Applicants vigorously traverse.

Applicants assert that the Examiner has failed to meet the burden that is imposed on the Examiner to explain why the claims are not enabled. The MPEP §2164.04 states regarding enablement rejections:

> *"it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." In re Marzocchi*,169 USPQ 367, 370 (CCPA 1971).

Applicants assert that the Examiner is simply making conclusory statements without any evidentiary basis and thus has failed to meet the burden placed upon the Examiner. The Examiner has made no effort to back up the assertions with acceptable evidence or reasoning. No reason is given as to why the claims are not enabled.

Further, Applicants in the written description have shown an increase in xylitol production (please see Example 8, on page 34, line 26 and Fig. 4) and lysine production (Example 23, Table 4 on page 52), in addition to that of ethanol. Applicants are claiming a general method that improves the method of making such products. To make ethanol from xylose, lysine from glucose or any other particular product more reduced than pyruvate from

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OK

[redacted]

carbohydrate, certain PRODUCT-SPECIFIC properties must be introduced to or selected for in the production organism. In the background of the written description (see pages 1-4 and especially page 4, lines 1-7) it is explained that these processes have a common GENERAL problem (overproduction of NADP and NADH) that limits their efficiency. The instant disclosure discloses a general solution of this problem that improves their efficiency.

In addition to the examples disclosing how the instant invention improves ethanol production from both hexoses and pentoses, xylitol production from xylose, and lysine production from glucose, Example 24 teaches how to use the invention further to increase production of polyhydroxybutyrates by a genetically engineered *S. cerevisiae*. One of skill in the art would readily recognize polyhydroxybutyrate is a molecule that is more reduced than ethanol. Accordingly, Applicants have provided an example that shows that the claimed invention is a general procedure that works for a variety of molecules. OK

In summary, Applicants assert that a general method is disclosed that solves the unbalanced production of NADP and NADH in biotechnological processes where products are produced that are more reduced that pyruvate (page 4, lines 1-7). Applicants have further shown that the process works for the production of ethanol, xylitol and lysine. Accordingly, Applicants assert

that absent **any** evidence to the contrary that the claims are not enabled for their full scope, withdrawal of the rejection is warranted and respectfully requested.

Allowable Claims

The Examiner acknowledges that claims 25 and 26 are allowable if deposit information is provided. Thus, Applicants' representative acknowledges that:

1) during the pendency of the application, access to the public will be afforded to the Commissioner upon request,
2) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent,
3) the deposit will be maintained in a public repository for a period of 30 years or five years after the last request or for the effective life of the patent, whichever is longer, and
4) the deposit will be replaced if it should ever become inviable.

Conclusion

With the above remarks and amendments, it is believed that the claims, as they now stand, define patentable subject matter such that a passage of the instant invention to allowance is warranted. A Notice to that effect is earnestly solicited.

If any questions remain regarding the above matters, please contact Applicant's representative, Gerald M. Murphy, Jr., in the Washington metropolitan area at the phone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE WRITTEN DESCRIPTION:

The paragraph starting at line 4 on page 20 has been amended as follows:

This aspect of the invention is illustrated in Examples 19 to 23. *Corynebacterium glutamicum* was transformed with a gene from *Peptostreptococcus asaccharolyticus* encoding an NAD-dependent glutamate dehydrogenase. The transformed *Corynebacterium glutamicum* shows NAD-linked glutamate dehydrogenase activity, and this organism naturally possesses NADP-linked glutamate dehydrogenase activity. The transformed organism therefore possesses a dehydrogenase pair according to the first embodiment of the invention that can convert NADP plus NADH into NAD plus NADPH. Unlike some bacteria, *Corynebacterium glutamicum* does not contain NADP/NADH transhydrogenase, so the sequential operation of the two glutamate dehydrogenases provides the bacterium with the novel means to equilibrate the NAD/NADH amd NADP/NADPH coenzyme couples. It is well known that the synthesis of lysine (and most other amino acids) [produces NADPH, and that when lysine is overproduced in large amounts the requirement for reoxidation of NADPH to NADP can limit the amino acid production] produces NADP, and when lysine is overproduced in large amounts the requirement for reduction of NADP to NADPH

can limit amino acid production. It is also known under the cultivation conditions used in Example 23, production of lysine does not begin while threonine is still present in the medium and that yields are relatively low until the bacteria stops growing (Vallino, J.J. [1991]; see [expecially] especially pages 207 to 213). Surprisingly, *Corynebacterium glutamicum* transformed according to the invention already produced large amounts of lysine while threonine was still present and before the bacterium had reached even 25% of the expected biomass yield. These examples disclose that the present invention can be [practised] practiced with advantage also in bacteria as well as fungi and for improving the production of amino acids as well as non-nitrogenous compounds such as ethanol and xylitol.